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(71) Applicant *(for all designated States except US)*: **NORTHEASTERN UNIVERSITY** [US/US]; 360 Huntington Avenue, Boston, MA 02115 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LAZAR, Iuliana, M.** [RO/US]; 1000F Spring Valley Drive, Andover, MA 01810 (US). **KARGER, Barry, L.** [US/US]; 62 Deborah Road, Newton, MA 02459 (US).

(74) Agents: **HEINE, Holliday, C.** et al.; Weingarten, Schurgin, Gagnebin & Lebovici LLP, Ten Post Office Square, Boston, MA 02109 (US).

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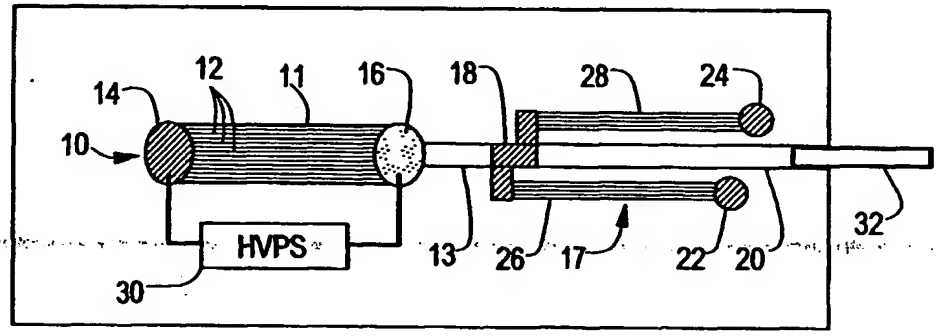
(54) Title: MICROCHIP INTEGRATED MULTICHANNEL ELECTROOSMOTIC PUMPING SYSTEM



(57) Abstract: A microchip integrated microfabricated, microfluidic, multichannel, preferably electroosmotic pump and pumping system is disclosed. The electroosmotic pump of the invention comprises a plurality of microchannels, which begin and end in common compartments, complexed into an array. The microchannels within the pump have substantially identical, optimal dimensions of cross-section and length such that sufficient pressure for optimal flow of fluid (e.g., liquid or gas) and pressure is generated by the pump and flow rates are stable and reproducible. To effectuate efficient flow of fluid without the hindrance of backpressure, an electroosmotic pump of the invention is coupled to a single channel of a larger cross-section. A similar structure is also used in an electroosmotic valve of the invention, where samples are introduced into an analytical device. The microfluidic electroosmotic pumping system of the invention generates sufficient flow and pressures by optimizing the dimensional parameters of cross-section and length to the microchannels.

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TITLE OF THE INVENTION

MICROCHIP INTEGRATED MULTICHANNEL ELECTROOSMOTIC PUMPING SYSTEM

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 60/292,780, filed May 22, 2001, entitled MICROCHIP INTEGRATED OPEN-CHANNEL ELECTROOSMOTIC PUMPING SYSTEM, the whole of which is hereby incorporated by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Part of the work leading to this invention was carried out with United States Government support provided under a grant from the National Institutes of Health, Grant No. GM15847. Therefore, the U.S. Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

Microfluidics and instrument miniaturization[1] have experienced significant growth in activity in recent years in response to the significant increase in use of microchips as bioanalytical tools. A major aspect of microfluidics refers to the manipulation of fluid flows in the microchip channels. For analytical processes, such as fluid valving,[2,3] mixing,[4] or electrically driven separations,[2-5] flow streams are typically generated using electrical forces (electroosmotic flow, or EOF). However, EOF is dependent on the surface charge of the channel walls and consequently is sensitive to the physicochemical properties of the sample (pH, ionic strength, organic content). For example, the EOF can be easily reduced or even suppressed if the channel surface is altered by contact with specific sample types. Alternatively, for some techniques such as micro-liquid

chromatography (μLC) or flow injection analysis (FIA), or for some samples, such as those containing cells that require zero electric field conditions for their manipulation, fluid flows on microchips may, or must, be generated by differential pressure.[6-8] Typically, this is accomplished by connecting external devices to the microchip, e.g., vacuum, gas pressure generators or syringe pumps. However, the connection of external devices to microchips, while effective, increases the complexity of the system, and integration and multiplexing capabilities may be compromised.

A number of micropumps have been described in the art. Mechanical pumps that use a membrane actuated by various forces (e.g., piezoelectric, electromagnetic, pneumatic)[9-15] are capable of pumping fluids of various physicochemical properties; however, the flow is pulsed, and the fabrication of the micropump is relatively complex. Non-mechanical pumps, with no moving parts, that operate on the basis of a large variety of principles (e.g., electrokinetic, centrifugal, electrohydrodynamic, etc.)[16-29] have been implemented. The flow produced by these pumps is generally pulse free and varies from a few nL/min to hundreds of μL/min. However, the generated pressures are low, up to only a few psi. Fabrication procedures are often complex, as well.

The use of electroosmosis for pressurized pumping was advanced almost forty years ago[30,31] and demonstrated later in open[32] and packed[16,17] capillary columns, and for open-channel microchip platforms.[18-22] While packed electroosmotic pumps were shown to be capable of generating both flow and pressure, having packed particles or porous materials within the pump structure may, *inter alia*, impose limitations on the pumping channel size, may necessitate additional steps in pump fabrication and may affect reproducibility from one pump to another. The open-channel configurations were capable of producing flow but not sufficient pressure for the intended applications. Accordingly, it would be useful to have a microchip-integrated pumping device that

simultaneously generates both sufficient flow and pressure for most analytical applications on a microchip and that is easy to fabricate, implement and use. Furthermore, an optimum pump design would ensure that a generated EOF is delivered to the analysis system and is not leaked out of the pump itself.

BRIEF SUMMARY OF THE INVENTION

The invention is directed to a microchip integrated microfabricated, microfluidic, multichannel, preferably electroosmotic pump and pumping system. The electroosmotic pump of the invention comprises a plurality of microchannels, which begin and end in common compartments, complexed into an array. The microchannels within the pump have substantially identical, optimal dimensions of cross-section and length such that sufficient pressure for optimal flow of fluid (e.g., liquid or gas) and pressure is generated by the pump and flow rates are stable and reproducible. In one aspect, the microchannels of the electroosmotic pump of the invention are open channels, i.e., not containing packed or porous materials. To effectuate efficient flow of fluid without the hindrance of backpressure, an electroosmotic pump of the invention is coupled to a single channel of a larger cross-section. A similar structure is also used in an electroosmotic valve of the invention, where samples are introduced into an analytical device. The microfluidic electroosmotic pumping system of the invention generates sufficient flow and pressures by optimizing the dimensional parameters of cross-section and length of the microchannels.

BRIEF DESCRIPTION OF THE FIGURES

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof and from the claims, taken in conjunction with the accompanying drawings, in which:

FIG. 1 shows a schematic diagram of the microfabricated electroosmotic pumping system in accordance with the invention;

FIG. 2 shows a schematic diagram of a different embodiment of the microfabricated electroosmotic pumping system in accordance with the invention;

FIG. 3A shows representative flow, diameter and length in a schematic representation of a micropump with one pumping channel;

FIG. 3B shows a graph of the flow distribution, or the F/F_{eof} coefficients calculated for a micropump with one microchannel at various d_1/d_2 ratios;

FIG. 4A shows a schematic representation of a micropump with n pumping channels;

FIG. 4B shows a graph of the flow distribution, or the F/F_{eof} coefficients calculated for a micropump with n microchannels at $d_1/d_2 = 0.1$;

FIG. 5A shows a graph of a total forward flow generated in a pumping system with $d_1/d_2 = 0.1$ and $L_1/L_2 = 0.1$ with varying number of pumping channels;

FIG. 5B shows a graph of a total forward flow generated in a pumping system with $d_1/d_2 = 0.1$ and $L_1/L_2 = 0.001$ with varying number of pumping channels;

FIG. 6A shows a graph of achievable pressure as a function of the micropump channel diameter, for a restriction with $d_2 = 30$ μm diameter ($L_1 = 0.03$ m, $L_2 = 30$ m, U = 3000 V);

FIG. 6B shows a graph of achievable pressure as a function of the micropump channel diameter, for a restriction with $d_2 = 50$ μm diameter ($L_1 = 0.03$ m, $L_2 = 30$ m, U = 3000 V);

FIG. 7A shows a schematic diagram of an injection of a well delimited sample plug moving through the electroosmotic valve of the invention;

FIG. 7B shows a schematic diagram of a sample plug being transported down the channel in the electroosmotic valve of the invention;

FIG. 8A shows a schematic diagram of an electroosmotic pumping system functioning as an electroosmotic valve;

FIG. 8B shows a schematic diagram of an electroosmotic pumping system functioning as an electroosmotic valve;

FIG. 9 shows an exemplary multiplexed pumping system in accordance with the invention; and

FIG. 10A and FIG. 10B show a cross-sectional view and a plan view, respectively, of a micropump according to the invention having filtering and gating elements.

DETAILED DESCRIPTION OF THE INVENTION

The microfabricated microfluidic pumping system of the invention comprises one or more miniaturized pumping units, which are capable of stable fluid delivery at flow rates and backpressures compatible with common analytical applications carried out on a microchip and sufficiently small to enable multiplexing of individual pumps. A multiple channel micropump based on electroosmotic pumping principles in accordance with the invention comprises a plurality of parallel, small cross-section microchannels (e.g., narrow or shallow) that deliver fluid to a microchannel of larger cross-section. This design allows the simultaneous generation of both flow and pressure and can be implemented in both packed channel and open-channel configuration. In the context of this invention, an open-channel means that no packed particles or porous materials are added to or contained in the microchannels. The pumping system of the invention offers numerous advantages. First, it can easily be integrated on microfluidic platforms and utilized for fluid propulsion on a microchip. Secondly, its fabrication using standard photolithographic and wet chemical etching technologies

(or other microelectromechanical systems (MEMS) technologies) ensures high manufacturing and operating reproducibility. Thirdly, the simplicity of the design ensures robustness, reliability and trouble free operation.

To illustrate the utility of an electroosmotic pumping system according to the invention, the micropump is designed to fit into an integrated microfluidic analysis scheme for delivery of, e.g., peptide samples for, e.g., electrospray ionization-mass spectrometry (ESI-MS) analysis. In addition, the ability to reproducibly control very low flow rates, at low and high pressure drops, where conventional systems do not perform well, enables the utilization of the micropump for many other micro-total analysis systems (μ-TAS) applications. The principle of μ-TAS is based on integrating all necessary parts and methods for analysis in miniaturized devices. The benefits of miniaturizing an analysis system include, but are not limited to, generation of multiple units at low cost; reduction in sample and reagent consumption and waste production; high throughput assays; small compact design; simple and reliable operation; and integration of several units or with existing systems.

Generally, the micropump of the invention can be used to deliver fluid flows in electric field free regions and perform sample transfer, gradient generation, or fraction collection/deposition. A large variety of applications can be envisioned for a micropump according to the invention, including, *inter alia*, eluent flow and/or pressure generation for condensed phase separation techniques (e.g., micro liquid chromatography in open, packed, monolithic or microfabricated channels, pressure assisted capillary electrochromatography or capillary electrophoresis, isoelectric focusing, affinity chromatography, immunoassays); single, parallel or sequential sample delivery for electrospray ionization-mass spectrometry (ESI-MS), matrix assisted laser desorption ionization (MALDI)-MS, optical

detectors, or other detection systems; single, parallel or sequential sample delivery systems to microreactors, mixers, preconcentrators, filters, or other functional elements integrated on the microchip; single, parallel or sequential eluent or sample delivery systems to off-chip applications; solvent gradient generation for on or off-chip applications; solvent and reagent delivery for flow injection analysis; sample or sample fraction generation/dispensing/collection from microfluidic systems; sample or sample fraction deposition on MALDI-MS targets; sample transfer/delivery to, or from, combinatorial libraries; sample delivery for medical applications (external or animal implanted devices); generation of microreactors or sample alteration devices by chemically or physically modifying the surface of the micropuming channel walls, while simultaneously maintaining pumping capabilities; generation of multiplexed devices for high throughput screening by integration of a series of pumps on one single microchip platform; and generation of pressure or vacuum in a liquid or gas phase within a microfluidic device, or an attached additional device.

FIG. 1 illustrates a simplified schematic drawing of an exemplary microfabricated electroosmotic pumping system of the invention. A pumping unit 10 can be incorporated on one microchip device. However, multiple pumping units can also be incorporated, e.g., in parallel as shown in FIG. 2 and FIG. 9. The microchip device may be about a few square millimeters, e.g., 5-50 mm^2. A multiplexed device (*see, e.g.*, FIG. 9) that may contain, for example, eight, sixteen, or even 96 individual pumps may require a larger size chip. Pumping channel system 11 of pumping unit 10 comprises a plurality of first shallow microchannels 12 (e.g., 2-10,000 microchannels). All pumping channels 12 have first and second ends, which are in fluid communication with a common inlet 14 and a common outlet compartment or reservoir 16, respectively. Electrodes inserted

in reservoirs 14 and 16 are connected to high voltage power supply 30 and are used to apply a voltage drop across the pump. The pumping channels are exposed only to buffer solutions and do not come in contact with any sample that may be added to the microchip. The pump size is quite variable and depends on the application (e.g., 1x10, 2x10, 5x50, 1x50 mm). The length of each microchannel may range from, e.g., about 5-50 mm. The channel depth, width, equivalent diameter or cross-section may range from about less than 1 μm to a few micrometers (e.g., 0.5-10 μm). The number of microchannels in one pump may range from two to more than a thousand (e.g., 2-10,000 channels). The spacing between the microchannels is in the low micrometer range (e.g., 1-50 μm). In one aspect, the pump unit of the invention comprises 4 microchannels, 10 microchannels, 25 microchannels, 100 microchannels or 1000 microchannels.

The pumping (or valve) system of the invention is activated by introducing into the channels a buffer or solvent, appropriate for preserving or increasing the surface charge on the pumping channel walls. The microchannels 12 can be filled by capillary action or by action of a pressure differential. Through electrodes placed in the reservoirs 14 and 16, a potential differential is applied across the microchannels 12. Depending on the surface properties of the channel (whether negatively or positively charged), the larger voltage must be applied to the appropriate reservoir, such that the electroosmotic flow will have the desired direction. For example, for a glass micropump having uncoated pumping channel walls, by applying a 2000 V on reservoir 14 and connecting reservoir 16 to ground, electroosmotic flow will be generated from reservoir 14 in the direction of reservoir 16. Electroosmotic flow is created due to the following mechanism. The functional groups on the pumping microchannel walls ionize in the presence of the solvent/fluid that is filling the microchannels and attract a layer of oppositely charged ions. When the potential

differential is applied, this layer of oppositely charged ions start to move in the direction of the appropriate electrode (negative electrode for positively charged ions), dragging along bulk fluid flow. If this electroosmotic flow is restricted from evolving freely by the structure of the system or by the rest of the microfluidic channel network on the chip, pressure will be created inside the microfluidic structure, and the electroosmotic flow will be distributed through all the channels of the device through a pressure controlled mechanism. By reversing the polarity on the electrodes in reservoir 14 and 16, the direction of pumping will be reversed, and the pump will draw fluid out from the rest of the channels.

The pumping system delivers fluid via a common outlet compartment, connected to reservoir 16, to larger diameter second microchannel 13, which may be connected to a network of channels or to other devices. As shown in FIGs. 1, 7 and 8, second microchannel 13 is connected to network channel 20 for, e.g., sample infusion or separation. Channel 20 comprises electroosmotic valve 17 of the invention, which is used, e.g., for sample introduction. The electroosmotic valve is open to electroosmotic driven flows and essentially closed to pressure driven flows. At the other end of the network channel 20, an electrospray emitter 32, for example, or a detection or a sample collection device using any of the systems described above, can be integrated for analysis of a sample.

Sample injection in a microfabricated analysis systems is accomplished electrokinetically[2,3] or by pressure gradients,[44] and sample manipulations are performed with electrokinetic forces. If sample manipulations are to be performed using pressure driven flows, a fluid valving system, such as described here, is necessary to prevent leakage of the fluid flow into the sample or sample waste reservoirs. According to the invention, electroosmotic valving is accomplished using very narrow channels

for the sample injection and waste lines, in a configuration similar to that of the electooosmotic pump. In a pressurized analysis system, narrow injection channels[45] can act as efficient valving components. As shown in FIG. 1, 7 and 8, in a valve according to the invention, a sample can be infused electroosmotically from reservoir 22 to reservoir 24 through the sample and sample waste pluralities off channels, 26 and 28, respectively, and a double-T injector 18.[46] The double-T injector can be an open or packed channel, e.g., as part of a preconcentration or μLC system. After completion of the injection, the pump can be started. For sample introduction and waste channels with similar dimensions to the pumping microchannels, additional pressure driven fluid loss through these channels could be negligible. Theoretically, if the number of injection and waste channels equals the number of pumping channels, the coefficient F/F_{eof} would be unaffected by the injection/waste channels when $d_1/d_2 = 0.01$, and would drop to only 50 % of its original value when $d_1/d_2 = 0.1$ ($L_1:L_2 = 1:1000$ in both cases).

In operation of the electroosmotic valve (as shown in FIG. 7A), all the appropriate channels and reservoirs of valve 17 and pump 10 are first filled with an appropriate eluent. Sample is injected into the valve inlet reservoir 22, and a voltage drop is established between reservoirs 22 and 24 to allow for a sample plug to be loaded into microchannel 20. The sample is electroosmotically carried from reservoir 22 in the direction of reservoir 24 by the application of a potential difference, e.g., 2000 V, between reservoir 22 and reservoir 24. A very small voltage drop (e.g., 100 V) between pump reservoir 14 and pump reservoir 16 may be needed on the pump unit 12 as well to help focus the injected plug in the microchannel 20.

As depicted in FIG. 7B, for injecting the sample plug down the microchannel 20 for analysis, a large voltage drop, e.g., 2000 V, between reservoir 14 and reservoir 16 is applied to the pumping

unit 11. The electrodes in reservoirs 22 and 24 are maintained at the same value as the voltage on reservoir 16, or they are removed from these reservoirs, in order to suppress the electroosmotic flow in the direction of the sample and sample waste reservoirs. The voltage drop across the pump will generate electroosmotic flow in the pump and pressurized flow in the rest of the system. The large hydraulic resistance in the sample inlet and outlet channels will prevent back pressure leakage, or will allow for only a small flow leakage through these channels. Consequently, the sample plug will be transported only down the microchannel 20.

As shown in FIG. 8A, an electroosmotic pumping system composed of two parallel pumps can function, alternatively, as an electroosmotic valve, as well. One of the pumps, e.g., pump 10, is used for loading the sample, while the other pump, e.g., pump 100, is used for loading the eluent. Small, well delimited sample plugs, however, cannot be injected with this configuration.

In FIG. 8B, for injecting the plug for analysis, a large voltage drop is applied across pump 100, for example, 2000 V between reservoir 104 and reservoir 106. The voltage on reservoirs 14 and 16 is maintained at the same value as the voltage on reservoir 106, or the electrodes are removed from these reservoirs. The voltage drop across the pump 100 will generate electroosmotic flow in this pump, and pressurized flow in the rest of the system. For properly designed pumping channel diameters, the pressurized leakage flow through pump 12 will be minimal.

The potential differential for electroosmotic flow (EOF) generation is applied between the inlet and outlet reservoirs and may be provided by a power supply. Depending on the length of the pumping channels and the desired flow rate and pressure, the necessary voltage drop for the operation of the electroosmotic micropump may vary from a few tens to thousands of volts (e.g., 50-2000 V/cm).

In some configurations, outlet compartment or reservoir 16 can be common for systems with multiple pumps. Referring now to FIG. 10, a semi-permeable gate 34, that allows for an exchange of ions but not of the bulk eluent flow (liquid or gas), is created at the bottom of the outlet reservoir. The gate prevents EOF leakage in the direction of the exit electrode 35' placed in the outlet reservoir. For example, a porous glass disc (e.g., 5 mm in diameter, 0.8-1 mm in width, and 40-50 Å pore size, prepared by Chang Associates (Worcester, MA)) can be used as the gate, but other materials may be used, e.g., graphite, polymeric organic or inorganic membrane materials. While most reservoirs on a microchip are made of glass, reservoir 16 is fabricated from a PEEK external nut. The porous glass disc is secured (e.g., between two gasket elements) at the bottom of reservoir 16 with a corresponding internal nut. This arrangement provides for robustness and exchangeability of the porous glass disc. Since the pumping microchannels act as a filter, clogging of some of the channels can occur. To reduce this effect, a short filter element 36 (e.g., 100 μm in length), of the same size and density as the collection of pumping channels, can be introduced, preferably at each end of the pump. Filter elements 36 are spaced from the ends of the pumping channels by intermediate compartments 38 and terminate at end compartments 14' and 16', respectively. In the embodiment shown, end compartments 14', 16' are connected to orifaces 40 in the substrate, which make connection with reservoirs 14 and 16 on the exterior surface of the substrate.

The pump can be fabricated in a variety of substrate materials such as, *inter alia*, glass, quartz, silicon, polysilicon, polymeric materials (organic or inorganic), ceramic, or other materials. The micropumps can be made using microfabrication techniques, for example, photolithography and wet chemical etching, or other microelectromechanical systems (MEMS)

technologies (e.g., dry etching, laser ablation, injection molding, embossing, stamping).

Microfabricated devices that contain an electroosmotic micropump of the invention can be fabricated from one or two substrates made of any of the materials described above. The microfluidic channels can be made using one of the substrates described above by any of the microfabrication techniques. For example, micropump and sample handling channels defined on a photomask by 2 and 20 μm wide lines (other dimensions are possible) are transferred to the substrate using photolithography. After exposure, substrate etching is conducted to achieve channel depths of 0.5-10 μm for the micropump and 20-100 μm for sample handling. This substrate is placed into contact with the second (or top) substrate such that the surface of the second substrate is covering the channels of the first substrate. The two substrates are then bonded together to seal the enclosed channels. Alternatively, the micropump channels may be fabricated in the bottom substrate, while the rest of the microfluidic network of channels and chambers may be fabricated in the top substrate, made of the same or a different material as the bottom substrate. They come in contact with each other by proper alignment prior to bonding. Alternatively, the micropump may be fabricated in a substrate that is sandwiched between other two substrates.

The walls of the pumping channels may be the bare, unmodified surface or the chemically/physically altered surface of the substrate material that is used for the fabrication of the device. In the case of certain substrate materials, chemical treatment with, or physical adsorption of an appropriate surface coating agent on the pumping channel walls, may be necessary in order to provide for sufficient and adequate charged functional groups on these walls.

The holes or the apertures necessary to access the pumping channel and the other channels of the microfabricated device are

fabricated prior to bonding in one or both of the substrates. These holes (typically of 1-2 mm in diameter) are used for the introduction of fluids and reagents into the chip, and for the placement of electrodes that ensure electrical contact with the network of microfluidic channels. These holes can also function as reservoirs for the solvent and reagents that are to be manipulated on the chip. To increase the volume of solvent or reagents that may be handled by the chip, additional reservoir structures may be attached to the access holes. Cooling or heating devices may be attached to the pump for specific applications.

Alternatively, in order to increase the resistance to back flow leakage, the straight microchannels can be replace by a tortuous arrangement, or even a more complicated microfabricated monolithic structure.

Alternatively, the electrodes may be embedded in the microfabricated device at appropriate positions. Embedded electrodes are fabricated using MEMS technologies prior to bonding of the two substrates.

Alternatively, the inlet and outlet reservoirs may be placed not directly on the pump inlet or outlet, but at the terminus of some larger channels, with small electrical resistance, that come in direct contact with the inlet and outlet of the pumping channels.

Alternatively, a structure (porous or multiple channel structure, etc.) with similar properties to the semi-permeable glass disc that is inserted in the outlet reservoir, can be created by MEMS technologies directly in the microchip body, at appropriate positions. This alternate gate structure can be used as fabricated, or it may be filled before utilization with an electrically conductive polymer that is replaceable. It will have the same function, to allow the exchange of ions but prevent transport of bulk flow.

Alternatively, in the case of configurations with two pumping units, the walls of the pumping microchannels of one or both pumps may be chemically or physically altered such that their surface is positively charged in the case of one of the pumps and negatively charged in the case of the second pump. Thus, by applying a potential differential between the two inlet reservoirs, 14 and 104, both pumps will generate electroosmotic flow in the same direction, but one will function under a positive voltage gradient, while the other will function under a negative voltage gradient. This configuration eliminates the need for the outlet reservoir 16 and the semi-permeable gate.

In another embodiment, the electrospraying or sample deposition capillary 32 may be replaced by a structure fabricated by MEMS technologies.

As shown in FIG. 2, to apply an eluent gradient with multiple pumps, e.g., two pumps 10 and 100, microchannels are filled with solvent or buffer. The solvent or buffer (SA) in reservoir 104 is replaced with a different solvent or buffer (SB). A porous glass disc 34 is placed and secured in reservoir 16 and 106. An identical voltage is applied to both reservoir 16 and 106. Voltages are then applied to reservoir 14 and 104 in a ratio that will provide the desired solvent mixture. The ratio of the two voltages is modulated (in steps or continuously) to generate a desired solvent gradient that is delivered to the system. The generated flow or pressure is monitored or measured.

In the present invention, a pump with a large number of narrow or shallow open microchannels is designed to produce EOF. Advantageously, the multiple microchannels ensure the generation of sufficient flow rate, while the small dimensions of the microchannels result in the necessary hydraulic resistance to pressurized back flow leakage. In contrast, a single, large diameter open-channel electroosmotic micropump could generate flow only if the backpressure is small, and the flow would be

highly dependent on the backpressure.[37] Properly designed, multiple channel pump configurations with small diameters according to the invention overcome this shortcoming, being capable of generating sufficient flow that is independent of backpressure. The pumping principles are further explained below.

Electroosmotic flow generation in single channels. To illustrate the principle of the open-channel electroosmotic micropump, an ideal system composed of cylindrical capillaries is considered and the conditions that must be met for proper pumping are examined. For this discussion, the contributions of local hydraulic resistances to the total pressure drop will be neglected. The standard equations that describe fluid flow and velocity in pressure driven ($F_{\Delta p}$ and $v_{\Delta p}$) and electroosmotic driven (F_{eof} and v_{eof}) open capillary systems are as follows:[38]

(1) $$F_{\Delta p} = \frac{\pi}{128\eta}\frac{\Delta p}{L}d^4$$

(2) $$v_{\Delta p} = \frac{1}{32\eta}\frac{\Delta p}{L}d^2$$

(3) $$F_{eof} = \frac{\pi\varepsilon_o\varepsilon_r\zeta}{4\eta}\frac{U}{L}d^2$$

(4) $$v_{eof} = \frac{\varepsilon_o\varepsilon_r\zeta}{\eta}\frac{U}{L}$$

where Δp = the pressure drop across a capillary of diameter d and length L, η = the viscosity of the fluid, ε_o = the electrical permitivity of the vacuum, ε_r = the relative permitivity of the medium (or dielectric constant), ζ = the zeta potential at the capillary wall, and U = the voltage applied across the capillary of length L. From equations (1) and (3), it can be seen that $F_{\Delta p}$ (Poisseuille flow) and F_{eof} (electroosmotic flow) are dependent on d^4 and on d^2, respectively, due to the fact that $v_{\Delta p}$ is

dependent on d^2, while v_{eof} is independent of d. Therefore, if fluid flow generation and distribution in a microfluidic structure occurs by both Δp and EOF, a net fluid flow to be induced in preferential directions is expected.

Consider a system comprised of a single narrow channel (I) with dimensions d_1 and L_1 connected to a large channel (II) with dimensions d_2 and L_2 (Figure 3A). If a potential drop is applied only to the narrow channel to generate flow through an electroosmotic mechanism (i.e., ~ d_1^2), the flow in both channels can be redistributed through a pressure-controlled mechanism (i.e., ~ d_1^4 and d_2^4). Pressure generation is due to the fact that the field free capillary (II) acts as a restrictor for the F_{eof} that is produced in capillary (I) under the influence of the electric field. The F_{eof} will distribute into a forward flow through the large channel (F) and a back flow through the narrow channel (F_b). Pressurized fluid flow will be proportional to d_1^4/d_2^4 regardless of the method used to produce it. Practically, for a ratio of d_1/d_2 of only 1:10 (L_1 being equal to L_2), the flow will be distributed in a ratio F/F_b of 1:10,000, i.e., essentially all the flow will be directed through the large channel.

When both pressure and a potential gradient are applied to a capillary, the resulting flow is a sum of the Poiseuille and electroosmotic flows.[30] By balancing the electroosmotic input flow (F_{eof}) given by equation (3) with the pressurized output flows (F and F_b) given by equation (1), it can be shown that the pressurized forward flow (F) in the large channel is dependent on the EOF in the narrow channel (F_{eof}), according to the following equation:

$$F = F_{eof} \frac{\frac{L_1}{L_2}}{\frac{L_1}{L_2} + \left(\frac{d_1}{d_2}\right)^4} \quad (5)$$

The F/F_{eof} ratio seems to be dependent on channel dimensions, but independent of pressure or the actual EOF in the system. F/F_{eof} could be defined as an efficiency coefficient for a given pump, since it will determine what fraction of the originally produced EOF is actually pumped forward in the system. F/F_{eof} values can be calculated from equation (5) and represented as a function of d_1/d_2 and L_1/L_2 (Figure 3B). As seen, in this figure, small diameter and long pumping channels (i.e., small d_1/d_2 and large L_1/L_2 ratios), result in large F/F_{eof} values and a more efficient electroosmotic pump. For example, for d_1/d_2 = 0.1, a relatively effective pump is created, since the F/F_{eof} coefficient decreases from 1 to only 0.9 even when the large channel is very long and imposes a considerable backpressure (L_1/L_2 = 0.001).

Electroosmotic flow generation in multiple channels. For very small d_1 values, the actual EOF in a channel and consequently the overall flow in the system will be quite low. For a channel diameter of 1 μm, the EOF will be 0.17 nL/min [calculated from equation (3) for a capillary with L_1 = 0.03 m and U=3000 V, and for parameters given in reference 45: ε_o = 8.85 x 10^{-12} C^2 N^{-1} m^{-2}, ε_r = 80, ζ = 50 x 10^{-3} V, and η = 0.001 N s m^{-2}]. In order to compensate for this low EOF, multiple small diameter channels (n) can be connected to one large channel (Figure 4A). However, in this case, by balancing again the flows, F will be defined by equation (6), and F/F_{eof} will be dependent on n:

$$(6) \quad F = F_{eof} \frac{\frac{L_1}{L_2}}{\frac{L_1}{L_2} + n\left(\frac{d_1}{d_2}\right)^4}$$

The larger n, the greater the total F_{eof}, but F/F_{eof} becomes smaller. F/F_{eof} values are represented as a function of n and L_1/L_2 for d_1/d_2 = 0.1 in Figure 4B. For example, for d_1/d_2 = 0.1 and L_1/L_2

= 0.001, the F/F_{eof} ratio drops from 0.9 to 0.09 when n is increased from 1 to 100.

The optimum number (n) and dimensions (d_1 and L_1) of the micropump channels that can generate the desired flow in the main channel can be calculated. If F/F_{eof} is determined from equation (6) and multiply this value with the total EOF value calculated according to equation (3), diagrams that show the total pressure driven flow for given system characteristics (in this case d_1/d_2 = 0.1) can be constructed (Figure 5). As expected, the total flow rate increases with the increase of d_1 and n. However, it is important to observe that when the backpressure increases significantly (i.e., L_2 becomes much larger than L_1), supplementing the pump with additional microchannels does not bring any additional benefit in increasing the flow rate (compare Figure 5B and Figure 5A). At high backpressures, the flow cannot be pumped, but rather will leak backwards in proportion to the number of channels n. The beneficial effect of increasing the number of microchannels requires properly chosen dimensions. At progressively smaller d_1/d_2 ratios, the back flow leakage becomes negligible. For example, as shown in Table 1, the F/F_{eof} coefficients maintain a high and relatively constant value for a large range of pumping microchannels when d_1/d_2 drops to a value of 0.01. Based on the above considerations, and depending on the specific applications, micropumps with 100 to 1000 pumping channels of 1-3 μm in depth would perform as effective pumping systems on microfluidic platforms.

Table 1. Variation of F/F_{eof} coefficient with d_1/d_2 and n (L_1/L_2 = 0.001).

d_1/d_2	n=1	n=10	n=100	n=1000	n=10000
1	0.001	1E-04	1E-5	1E-6	1E-7
0.1	0.909	0.5	0.091	0.009	0.001
0.01	0.999	0.999	0.999	0.990	0.910

Electroosmotic pressure generation. The pressure that can be created in the system is calculated by balancing the input electroosmotic flow in the *n* narrow channels with the output pressure flow through all channels:

$$\Delta p = \frac{32 n \varepsilon_o \varepsilon_r \zeta \frac{U d_1^2}{L_1}}{n \frac{d_1^4}{L_1} + \frac{d_2^4}{L_2}} \quad (7)$$

A plot of this pressure as a function of pumping channel diameter, for given system characteristics, is shown in Figure 6. It is worth noting that the pressure depends on the number and dimensions of the pumping microchannels, the voltage applied to the pump, the zeta potential, and the relative permitivity of the medium. The pressure is, however, not dependent on the fluid viscosity. In a system with enhanced restriction, i.e., d_2 = 30 μm (Figure 6A), the pressure will be higher than in a system with a lower restriction, i.e., d_2 = 50 μm (Figure 6B). The condition of maximum pressure:

$$\frac{\partial P}{\partial d_1} = 0 \quad (8)$$

is accomplished when:

(9) $$\frac{nd_1^4}{L_1} = \frac{d_2^4}{L_2}$$

The absolute maximum pressure that can be generated with microchannels of a given dimension can be inferred from conditions of zero flow out from the system [i.e., the second term in the denominator of equation (7) is set to zero], and is dependent only on the channel diameter, applied voltage and channel surface properties:

(10) $$\Delta p_{max} = \frac{32\varepsilon_o \varepsilon \xi U}{d_1^2}$$

For a pump that would be used for a LC separation, once the parameters of the separation column (d_2, L_2) and the optimum eluent flow rate are determined, the pressure necessary to generate this flow can be calculated, and the appropriate pump configuration (n, d_1, and L_1) can be chosen from diagrams such as shown in Figures 5 or 6. For a packed column, d_2 and L_2 are the dimensions of an equivalent open tubular LC column that produces the same pressure drop. Alternatively, the d_2^4/L_2 ratio in the denominator of equation (7) could be replaced by a term that takes into consideration the porosity and the permeability of the column. The microchip implementation of fully integrated micro-LC separations performed on polymeric monolithic stationary phases that are commonly performed under 100 psi[39] thus becomes feasible with the integration of such pumping systems. Theoretically (see equation 10), if pressure generation and not flow were the main purpose of these micropumps, and if microchip material and connecting elements would be capable of withstanding the high pressures, hundreds of bars could be produced with sub-micrometer sized channel EOF pumps.

USE

A stand-alone microfabricated device with an integrated multichannel EOF pump according to the invention has been constructed for producing controllable pressure driven flows within microfluidic channels. If desired, the pump can be constructed as a stand-alone module and can be employed to deliver fluid flow for on-chip or off-chip applications, as well. Micropumps with 4-100 pumping channels were constructed that produced flow rates in the range of 10-400 nL/min and developed pressures up to 80 psi. The flow rate and eluent gradients were adjusted by varying the potential drop over the pump. The experimental results followed closely the trends predicted by the theoretical calculations.

The new approach for microfluidic valving according to the invention, e.g., "electroosmotic valving," in which sample plugs can be injected in pressurized systems, was tested for the investigation of peptide samples by MS analysis. The incorporation of an adsorbing medium for sample preconcentration in the double-T injector could prove useful in avoiding the electrophoretic bias effect, inherently associated with the use of electrokinetic forces for sample mobilization.

Two examples of system design to accomplish specific results follow:

Consider conducting a liquid chromatography separation in an open tubular capillary where the optimum separation parameters have been determined to be: d_2 = 20 μm, L_2 = 0.5 m, and F = 100 nL/min. The required pump design that can generate this flow rate in a liquid chromatography column can be determined from plots such as shown in FIG. 4A, which was constructed for d_1/d_2 = 0.1 and L_1/L_2 = 0.1. A pump with d_1 = 2 μm, L_1 = 0.05 m, and n = 200, would generate about 110 nL/min.

Consider conducting a liquid chromatography separation in a column filled with monolith packing. The optimum separation parameters are: d_2 = 150 μm, L_2 = 0.05 m, F = 700 nL/min, and the necessary pressure to generate this flow rate through the monolithic packing is about 3.4 bar. The equivalent column length that would generate a 3.4 bar pressure drop, at 700 nL/min and d_2 = 150 μm, is L_2 = 362 m. The appropriate pump design can be chosen, again from plots such as shown in FIG. 4A, or can be directly calculated. For instance, a pump with d_1 = 2 μm, L_1 = 0.05 m, and n = 2000, would generate a total F_{eof} = 1320 nL/min. For the selected parameters, one can determine d_1/d_2 = 0.013, L_1/L_2 = 1.38, and F/F_{eof} = 0.70. Consequently, F can be calculated. A flow of F = 910 nL/min will be produced, which is enough to drive the separation. Alternatively, a more efficient pump (d_1 = 1-1.5 μm) that would guarantee a larger F/F_{eof} coefficient could be chosen, as well.

In other embodiments, the electroosmotic pump according to the invention may be used with any other valving component, and the electroosmotic valve of the invention may be used with any other pump or pressure generating element (in particular, an electroosmotic/electrokinetic pump. The output of a pump and/or valve of the invention may be monitored via connection to a flow or pressure monitoring/controlling sensor and/or controller. A cluster of pumps may be attached to an individual network channel for, e.g., gradient generation or the introduction of a sequence of solvents into the system. A microfluidic device with a multiple channel structure constructed according to the invention allows for material transport driven by any mechanism (electric, magnetic, etc.) other than a pressure driven mechanism. Additionally, a microfluidic pump according to the invention can serve as an actuator for closing/opening of another valving component. The above microfluidic devices and pumps operate with

aqueous and/or organic solutions, or other fluids (e.g., any liquid or gas).

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While the present invention has been described in conjunction with a preferred embodiment, one of ordinary skill, after reading the foregoing specification, will be able to effect various changes, substitutions of equivalents, and other alterations to the compositions and methods set forth herein. It is therefore intended that the protection granted by Letters Patent hereon be limited only by the definitions contained in the appended claims and equivalents thereof.

CLAIMS

What is claimed is:

1. A microfluidic pump or valve device comprising:
a substrate, said substrate comprising:
a plurality of first microchannels, each of said first microchannels having a first and a second end, wherein said first ends of said first microchannels originate at a common inlet compartment and wherein said second ends of said first microchannels terminate at a common outlet compartment.

2. The microfluidic device of claim 1, wherein said first microchannels are open-channeled.

3. The microfluidic device of claim 1, wherein said plurality of first microchannels comprises at least 5 microchannels.

4. The microfluidic device of claim 1, wherein said plurality of first microchannels comprises at least 50 microchannels.

5. The microfluidic device of claim 1, wherein said plurality of first microchannels comprises at least 100 microchannels.

6. The microfluidic device of claim 1, wherein said plurality of first microchannels comprises at least 1,000 microchannels.

7. The microfluidic device of claim 1, wherein said plurality of first microchannels comprises at least 10,000 microchannels.

8. The microfluidic device of claim 1, wherein said plurality of first microchannels are in a substantially parallel configuration.

9. The microfluidic device of claim 1, wherein said plurality of first microchannels are in a tortuous configuration.

10. The microfluidic device of claim 1, said device further comprising an electrode embedded in said common outlet compartment.

11. The microfluidic device of claim 1, said device further comprising an electrode embedded in said common inlet compartment.

12. The microfluidic device of claim 1, said device further comprising an oriface connecting said inlet compartment to a surface of said substrate.

13. The microfluidic device of claim 1, said device further comprising an oriface connecting said outlet compartment to a surface of said substrate.

14. The microfluidic device of claim 1, said device further comprising a second microchannel coupled to said outlet compartment, wherein said second microchannel is larger in cross-section than an individual said first microchannel.

15. A microfluidic system configured in a substrate, said system comprising:

(a) an electroosmotic pump comprising:

(i) a plurality of first microchannels fabricated in said substrate, each of said first microchannels having a first and a second end, wherein said first ends of said first microchannels originate at a common inlet compartment and wherein said second ends of said first microchannels terminate at a common outlet compartment; and

(ii) a voltage source coupled to said inlet and outlet compartments for said first microchannels;

(b) a second microchannel, said second microchannel having a larger cross-section than each of said plurality of first microchannels, said second microchannel having first and second ends, wherein said common outlet compartment of said first microchannels is in fluid communication with said first end of said second microchannel; and

(c) an electroosmotic valve comprising:

(i) two sets of a plurality of third microchannels fabricated on said substrate, said third microchannels each having a smaller cross-section than said said second channel, each of said third microchannels having a first and a second end, wherein said first ends of said first set of a plurality of third microchannels originate at a common inlet compartment, wherein said second ends of said first set of a plurality of third microchannels is in fluid communication with said second microchannel, wherein said second ends of said second set of a plurality of third microchannels is also in fluid communication with said second microchannel and wherein said first ends of said second set of a plurality of third microchannels terminate at a common outlet compartment; and

(vi) a voltage source coupled to said inlet and outlet compartments.

16. The microfluidic system system of claim 15, wherein the ratio of the diameter of a said first microchannel to the diameter of said second microchannel is 1:1.25 - 1:1000.

17. The microfluidic system system of claim 15, wherein said substrate material is selected from the group consisting of glass,

quartz, silicon, polysilicon, polymeric materials (organic or inorganic) and ceramic.

18. The microfluidic system system of claim 15, wherein said outlet compartment associated with said plurality of first microchannels comprises a semi-permeable gate.

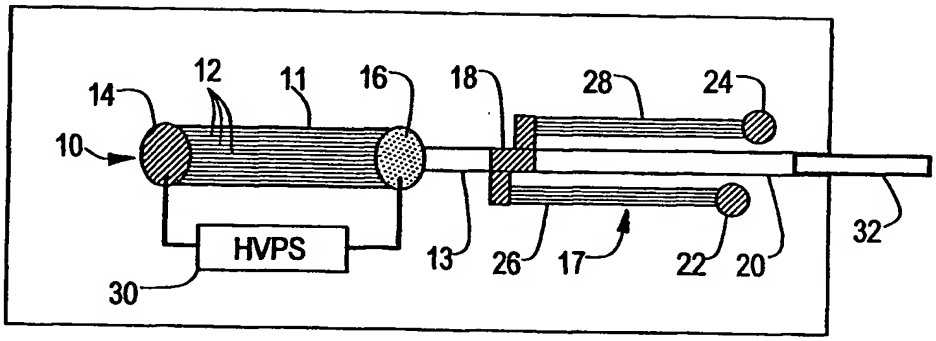
19. The microfluidic system system of claim 15, wherein said semi-permeable gate is selected from the group consisting of a porous glass, graphite, and polymeric organic or inorganic material.

20. A method of transporting a material for analysis through a microchannel in a microchip, said method comprising the steps of:

providing in said microchip a plurality of first microchannels and a second microchannel, wherein said second microchannel has a first and a second end, wherein the cross-section of each of said first microchannels is smaller than the cross-section of said second microchannel, wherein said first end of said second microchannel is in fluid communication with said plurality of first microchannels at one end of each and wherein said second end of said second microchannel is in communication with a dectection system for analysis of a sample;

introducing a sample into said second microchannel; and

applying a potential difference across a length of said plurality of microchannels to electroosmotically move said sample in said second microchannel.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12
11
16
18
28
24
10
HVPS
30
13
26
17
22
20
32

FIG. 1

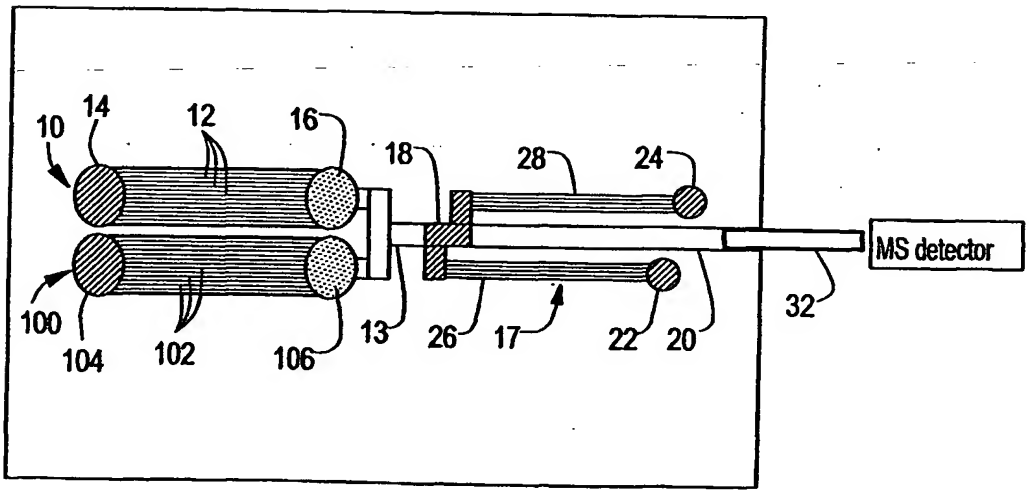
10
14
12
16
18
28
24
MS detector
100
104
102
106
13
26
17
22
20
32

FIG. 2

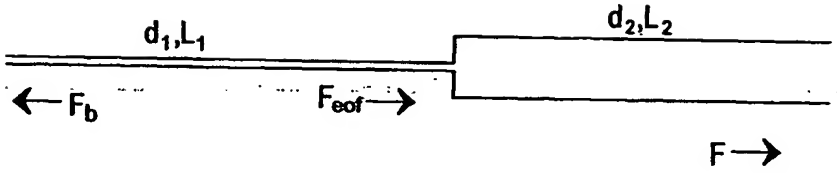
d1,L1
d2,L2
Fb
Feof
F

FIG. 3A

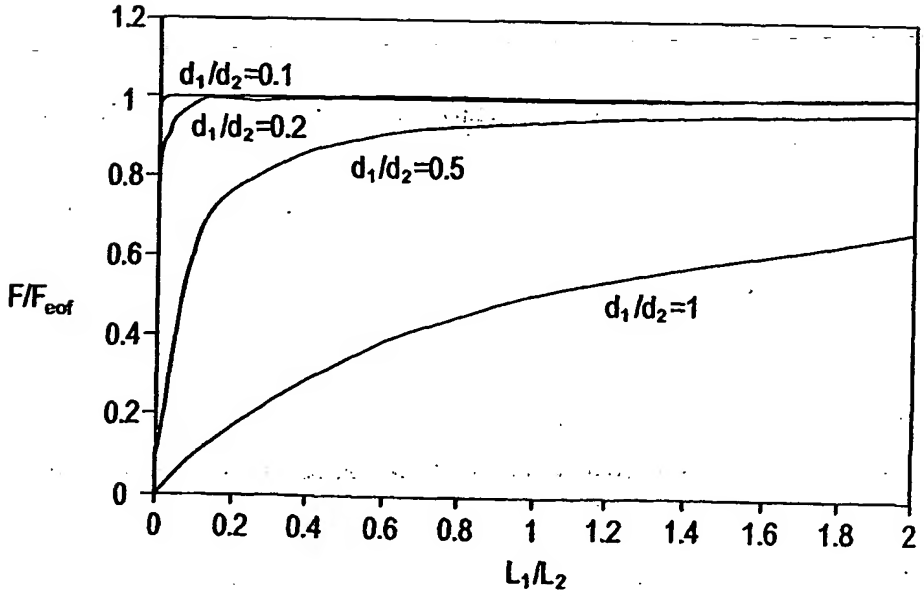
1.2
1
0.8
0.6
0.4
0.2
0
F/Feof
d1/d2=0.1
d1/d2=0.2
d1/d2=0.5
d1/d2=1
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
L1/L2

FIG. 3B

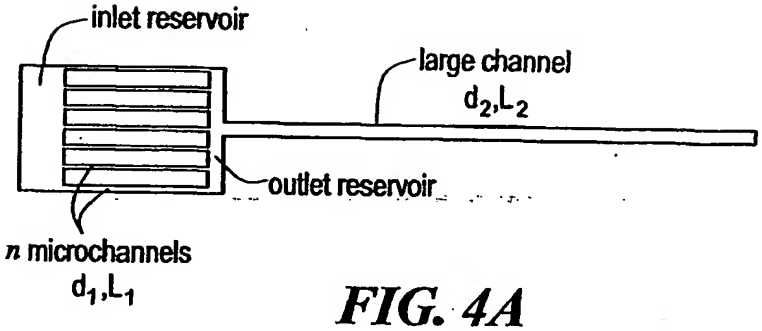
inlet reservoir
large channel
d_2, L_2
outlet reservoir
n microchannels
d_1, L_1

FIG. 4A

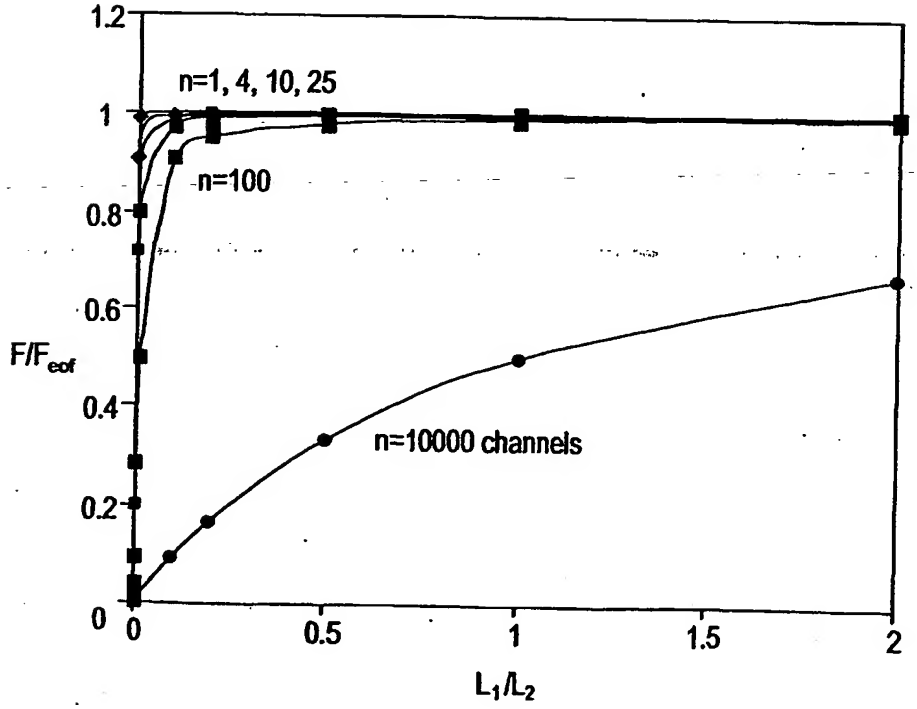
1.2
1
0.8
0.6
0.4
0.2
0
F/F_{eof}
n=1, 4, 10, 25
n=100
n=10000 channels
0
0.5
1
1.5
2
L_1/L_2

FIG. 4B

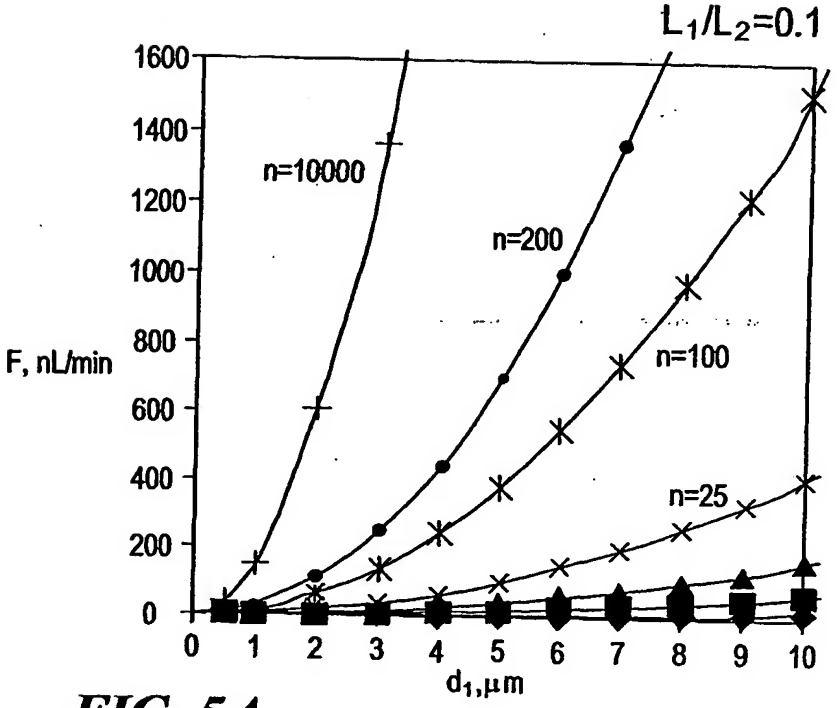
L1/L2=0.1
F, nL/min
d1,μm
n=10000
n=200
n=100
n=25
0
200
400
600
800
1000
1200
1400
1600
0 1 2 3 4 5 6 7 8 9 10

FIG. 5A

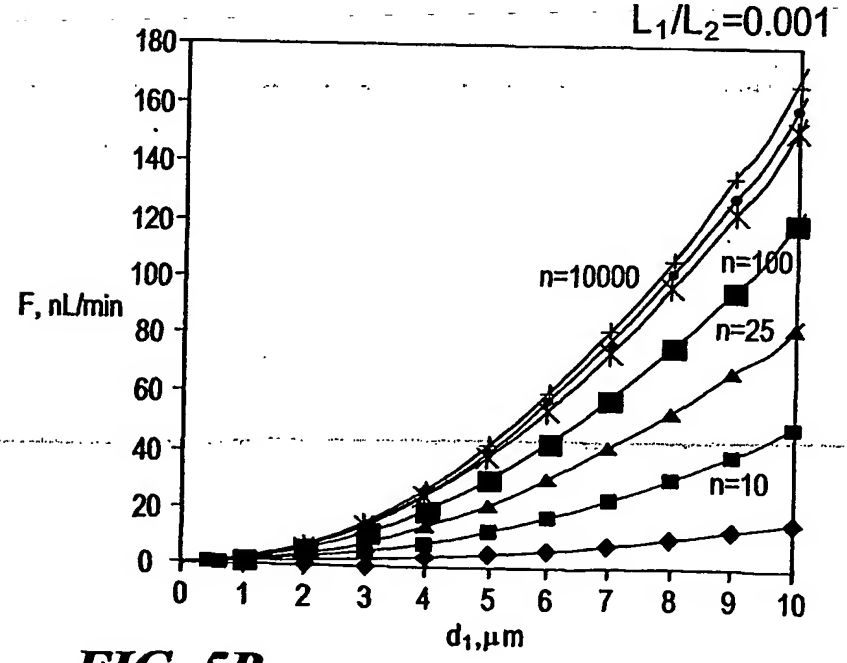
L1/L2=0.001
F, nL/min
d1,μm
n=10000
n=100
n=25
n=10
0
20
40
60
80
100
120
140
160
180
0 1 2 3 4 5 6 7 8 9 10

FIG. 5B

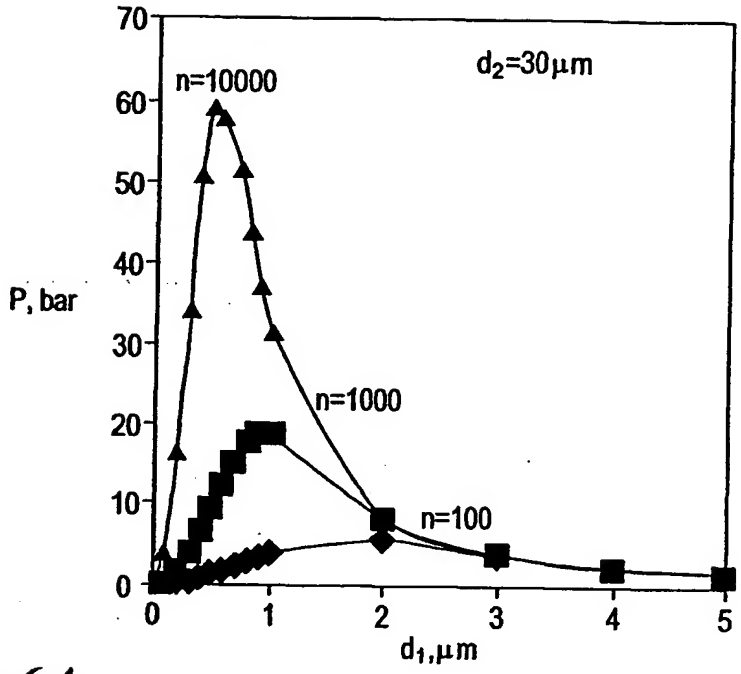
70
60
50
40
30
20
10
0
P, bar
n=10000
d_2=30μm
n=1000
n=100
0
1
2
3
4
5
d_1,μm

FIG. 6A

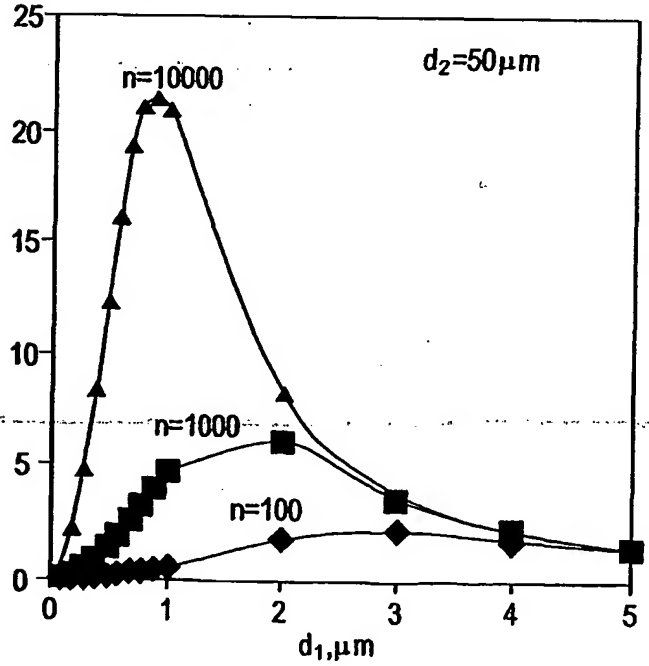
25
20
15
10
5
0
n=10000
d_2=50μm
n=1000
n=100
0
1
2
3
4
5
d_1,μm

FIG. 6B

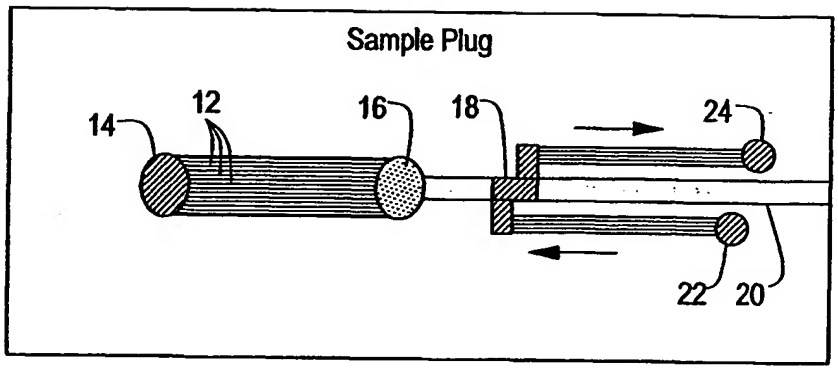

FIG. 7A

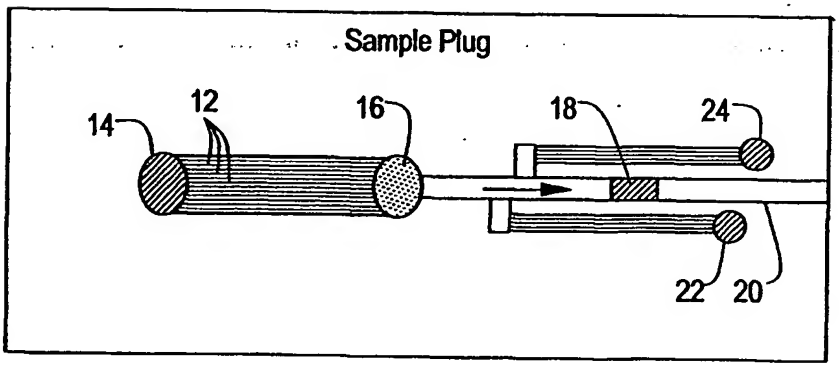

FIG. 7B

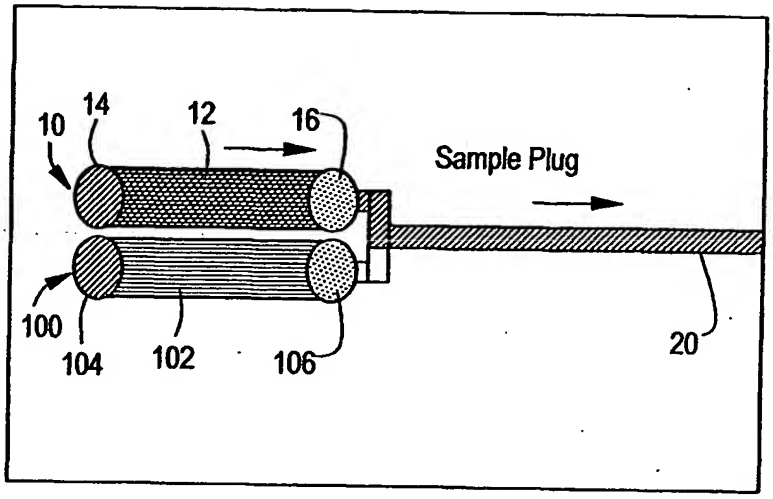
10
14
12
16
Sample Plug
100
104
102
106
20

FIG. 8A

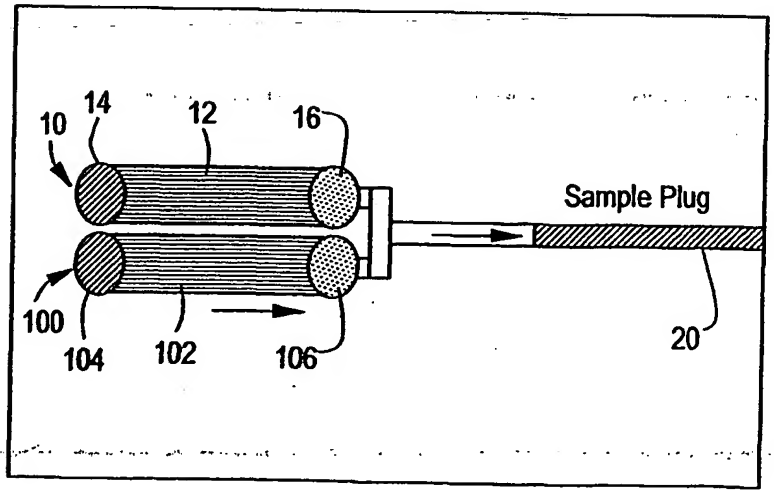
10
14
12
16
Sample Plug
100
104
102
106
20

FIG. 8B

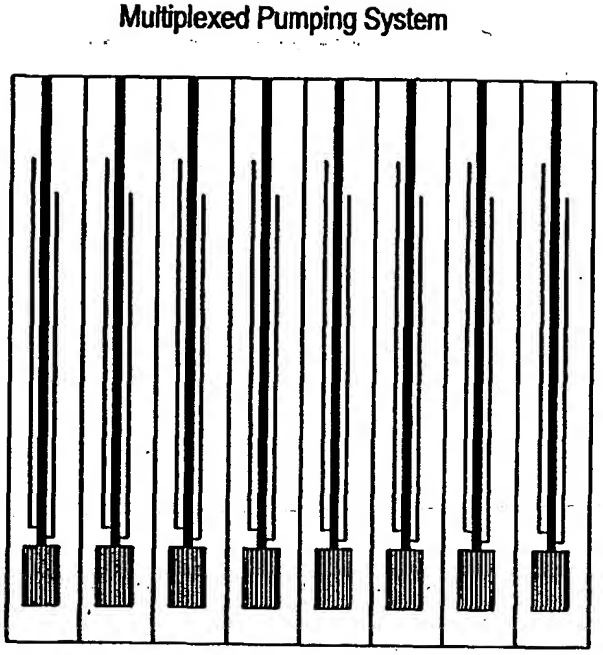

FIG. 9

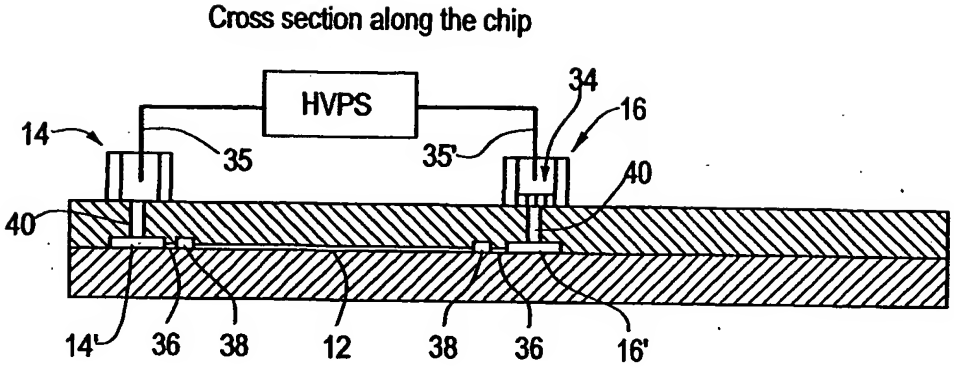

FIG. 10A

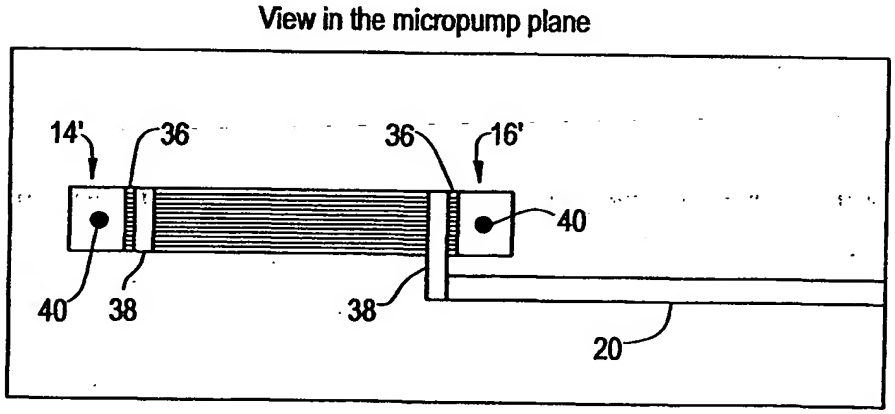

FIG. 10B